IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: John B. Harley

Serial No: 07/867,819 Art Unit: 1813

Filing date: April 13, 1992 Examiner: A.Caputa

For: METHODS AND REAGENTS FOR DIAGNOSIS OF AUTOANTIBODIES

Assistant Commissioner of Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the Office Action mailed August 15, 1995, finally rejecting claims 1-3 and 10-16. A Notice of Appeal was mailed January 12, 1996.

1. Real Party in Interest.

The real party in interest in the assignee, the Board of Regents of the University of Oklahoma, Oklahoma City, OK.

2. Related Appeals and Interferences.

There are no related appeals or interferences known at this time to appellant, the appellant's legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

3. Status of Claims

Claims 1-3 and 10-16, as amended in the Amendments mailed June 28, 1995, February 28, 1995, September 27, 1994,

March 21, 1994, and September 9, 1993, are pending. Claims 4-9 and 17-20 have been cancelled.

4. Status of Amendments.

No amendments were filed in response to the Office Action mailed August 15, 1995, finally rejecting the claims. The claims as pending on appeal are attached in an Appendix.

5. Summary of Invention.

Pending claims 1-3, 10 and 11 are drawn to specific peptides of less than forty amino acids, forming a linear epitope for a human autoantibody. Epitopes are regions of a few, typically four to seven, amino acids which are bound by the variable region of an antibody with great specificity. A linear epitope is a contiguous sequence of amino acids, as compared with a conformational epitope, which may be formed by the three dimensional folding or protein interaction by non-adjacent amino acids. Pending claims 12-16 are drawn to a method for screening patients for autoantibodies to Ro/SSA, an autoantigen in patients with systemic lupus erythematosus ("SLE"), by reacting any of the defined peptides of claims 1-3, 10 and 11, with a biological sample from a patient. If the autoantibodies are present in the sample, they will react with the claimed peptides in a detectable manner.

The peptides defined by the claims were determined empirically, as described in the application in Example 2 at

pages 16-18 of the application. Specifically, sequential peptides of eight contiguous amino acids of the Ro/SSA protein, a known autoantigen, were made and tested using sera from SLE patients for reactivity. The peptides consisted of amino acids 1-8, 2-9, 3-10, 4-11, etc. Non-elected species of the claims were drawn to peptides generated in the same manner from the La/SSB as described in Example 1, pages 10-16 of the application, for the 70 kD nuclear ribonuclearprotein, nRNP, as described in Example 3 at pages 19-20 of the application, and for the Sm B/B' protein as described in Example 4 at pages 20-27. As described in the application at pages 24-27, essential amino acids, and the effect of additions, substitutions, and deletions on binding of the various peptides was determined.

The presence of autoantibodies to Ro/SSA is diagnostic for autoimmune disease. Any antibodies to Ro/SSA are abnormal and associated with disease. Therefore, all of the claimed peptides are useful in predicting whether or not a patient has an autoimmune disease. The greater the levels of antibody to Ro/SSA, the worse the prognosis of the disease. See, for example, Harley, J.B., A.L. Sestak, L. Willis, S.M. Fu, J. Hanson, M. Reichlin "Model for Disease Heterogeneity in Systemic Lupus Erythematosus. Relationships between histocompatibility antigens, autoantigens, and lymphopenia on renal disease" (1989) Arthritis Rheumatism 39, 826-836 (copies in the record). The

advantages of the peptides include that they are considerably easier and therefore cheaper to make than natural autoantigen; the amount is easier and more accurately standardized for quantitation of autoantibody purposes; "epitope" spreading can be determined, which is not possible with natural protein; and it is easier to immobilize and label the small peptides as compared with the intact autoantigen. Epitope spreading is particularly important in view of the recent observations made possible based on the discovery of these peptides, which explain how patients initially produce autoantibody only to one to a few epitopes on the autoantigen, which increases to many epitopes over time, indicating the course of the disease in that patient.

6. Issues.

The issues on appeal are whether the claims are:

(a) Indefinite under 35 U.S.C. §112 as to the phrase "sequence of epitope" and what constitutes the minimum length of the peptide.

(b) Enabled by the specification under 35 U.S.C. §112, first paragraph;

(c) Obvious under 35 U.S.C. §103 over Deutscher, et al., Proc. Natl. Acad. Sci. USA 85, 9479-9483 (1988) in view of U.S. Patent No. 5,312,752 to Wotiz, et al., Voller, et al., Manual of Clin. Lab. Immunol. Chap. 17 (1986) and Geysen, et al. J. Immunol. Methods. 102, 259-271 (1987).

7. Grouping of Claims.

The claims do not stand or fall together. Claims 1-3, 10 and 11 are drawn to specific peptides.

Claims 12, 13, and 15 are drawn to the use of the claimed peptides in an assay for screening patients for the presence of autoantibodies.

Claim 16 requires the additional step of using the reactivity information to predict the prognosis of the patient.

Each of these groups has different elements which are not obvious over each other. Claim 16 in particular requires having observed using the peptides that epitope spreading occurs over time in patients having autoantibodies immunoreactive with the autoantigen from which the peptides are derived.

8. Arguments.

1. <u>The claims are definite under 35 U.S.C. §112, second paragraph.</u>

The claims have been rejected on two bases:

(a) the phrase "sequence of epitope" is indefinite; and

(b) what is the minimum length of the peptide.

(a) "Sequence of epitope" is readily understood.

As described throughout the application, especially in the examples, appellant determined which epitopes were significantly reactive with autoantibodies by synthesizing

octapeptides (i.e., peptides of eight amino acids) based on the known amino acid sequences of human autoantigens, in this case, the Ro/SSA antigen. Peptides were synthesized with contiguous amino acid sequences found in the native autoantigen, beginning with amino acids one to eight, then amino acids two to nine, then amino acids three to ten, and so on to the end of the protein. It is therefore clear from the language of the claim to one who has read the specification what this phrase means. Specifically, what is claimed is **a peptide forming a linear epitope for a human autoantibody . . . wherein the sequence of the epitope begins with the amino acid numbered from the amino terminus followed by the listed amino acid sequence.** Moreover, even if this phrase were unclear, it would be irrelevant since the actual amino acid sequence of the epitope is provided in the claim! The reference to the number is merely to the relative position of the epitope within the native protein.

(b) *The minimum length of the peptide is that which forms an epitope bound by an autoantibody as defined by the claim.*

The claims define the maximum length of the peptide as forty amino acids. The claims the minimum length of the claimed peptides as that "forming a linear epitope for a human autoantibody", *a priori*, at least five to eight amino acids,

which would be readily known and/or ascertainable as described in the application by one skilled in the art.

It is well established that antibodies bind to epitopes which are formed by five to eight amino acids; see, for example, "Molecular Biology of the Gene" Watson, et al., 4th edition, page 836 (Benjamin/Cummings Publishing Co. 1987), a copy of which is enclosed. As described in the application, each peptide epitope which is claimed **was actually identified by binding to autoantibodies in patient sera**; unlike many "biotech" cases, each of the claimed epitopes has actually been measured not only for binding but for significant binding (at least two standard deviations greater than normal sera; see, for example, page 19, first full paragraph, of the specification). Accordingly, not only is this a defined term which would be readily understood even by a laboratory technician of relatively low skill in the art, it would clearly be understood by one of ordinary skill in the art.

2. <u>The claims are enabled by the specification as required by 35 U.S.C. §112, first paragraph.</u>

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims to enable

one skilled in the pertinent art to make and use the claimed invention. The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 199 USPQ 659 (CCPA 1976). A patent need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). Whether undue experimentation is needed is not based upon a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been

summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) as follows:

(1) The quantity of experimentation necessary (time and expense);

(2) The amount of direction or guidance presented;

(3) The presence or absence of working examples of the invention;

(4) The nature of the invention;

(5) The state of the prior art;

(6) The relative skill of those in the art;

(7) The predictability or unpredictability of the art; and

(8) The breadth of the claims.

It is not necessary that every enablement analysis consider all of the factors.

Taking each of these factors in turn:

(1) There is no experimentation required since the specific epitopes are defined by the claims.

(2) There is explicit guidance not only specifically providing the amino acid sequences of the claimed epitopes but providing the data showing their actual reactivity with autoantibodies present in patient sera.

(3) As noted in (2), the peptides are all explicitly demonstrated to bind in working example 2 of the application.

(4) The nature of the invention is reagents for use in a diagnostic assay, and methods for use thereof.

(5 and 6) The prior art is replete with the same assays using purified protein or protein mixtures and other peptides in immunoassays.

(7) It is absolutely predictable that the epitopes will bind since they have all been identified based on their binding affinity for autoantibodies in patient sera.

(8) The claims are limited to peptides forming epitopes immunoreactive with autoantibodies which contain the defined amino acid sequences.

Since the only epitopes claimed are those that are linear or continuous, adding amino acids to the end(s) of the octapeptide should not alter binding. It is well established that peptides of forty or less amino acids do not fold to form tertiary structure which might inhibit access to the epitope. There is no support for the *allegation* that additions of amino acids to the peptide might prevent binding - applicants have indeed provided evidence that additions to the epitopes (much less the peptides), as well as minor deletions or substitutions - do not alter binding or have been identified and can be avoided. *See* pages 24 to 27 of the specification, providing actual binding data and analysis.

3. The claims are not obvious in view of the cited art.

a. The claimed invention.

As discussed above, pending claims 1-3, 10 and 11 are drawn to specific peptides of less than forty amino acids, forming a linear epitope for a human autoantibody. Epitopes are regions of a few, typically five to eight, amino acids which are bound by the variable region of an antibody with great specificity (see, for example, the references from General Immunology by Herman Eisen and Molecular Biology of the Gene by Watson, et al. enclosed with the amendment mailed February 28, 1995, copies enclosed in the appendix of this Brief). A linear epitope is a contiguous sequence of amino acids, as compared with a conformational epitope, which may be formed by the three dimensional folding or protein interaction by non-adjacent amino acids. As defined by the claims, the claimed peptides are those including an epitope of a defined amino acid sequence.

Pending claims 12-16 are drawn to a method for screening patients for autoantibodies to Ro/SSA, an autoantigen in patients with systemic lupus erythematosus ("SLE"), by reacting any of the defined peptides of claims 1-3, 10 and 11, with a biological sample from a patient. If the autoantibodies are present in the sample, they will react with the claimed peptides in a detectable manner.

The peptides defined by the claims were determined empirically, as described in the application in Example 2 at pages 16-18 of the application. Specifically, sequential peptides of eight contiguous amino acids of the Ro/SSA protein, a known autoantigen, were made and tested using sera from SLE patients for reactivity. The peptides consisted of amino acids 1-8, 2-9, 3-10, 4-11, etc. Non-elected species of the claims were drawn to peptides generated in the same manner from the La/SSB as described in Example 1, pages 10-16 of the application, for the 70 kD nuclear ribonuclearprotein, nRNP, as described in Example 3 at pages 19-20 of the application, and for the Sm B/B' protein as described in Example 4 at pages 20-27. As described in the application at pages 24-27, essential amino acids, and the effect of additions, substitutions, and deletions on binding of the various peptides was determined.

b. The cited art.

Claims 1-3 and 10-16 were rejected as obvious under 35 U.S.C. §103 over Deutscher, et al., Proc. Natl. Acad. Sci. USA 85, 9479-9483 (1988) in view of U.S. Patent No. 5,312,752 to Wotiz, et al., Voller, et al., Manual of Clin. Lab. Immunol. Chap. 17 (1986) and Geysen, et al. J. Immunol. Methods. 102, 259-271 (1987). It should be noted that this rejection was raised in the Office Action mailed October 19, 1993, and withdrawn in the

Office Action mailed June 27, 1994, then raised again in the Office Action mailed November 29, 1994.

Wotiz, et al.

Wotiz, et al., discloses antibodies immunoreactive with the DNA-binding domain of the estrogen receptor protein. The disclosure is specific to estrogen receptor proteins. The zinc finger referred to by the Examiner consists of a region of at least 40 amino acids. **Only a few amino acids are conserved in any claimed peptide.** Please note the use by Wotiz, et al., of the language at col. 16, lines 61-64, "furthermore, this region is ***thought*** *to have the conserved cysteine and histidine residues* which may be involved in the formation of the zinc-finger-like structures of the proteins". (emphasis added) Based on the Examiner's comments regarding the uniqueness of this region to the human estrogen receptor, and the **lack of crossreactivity of polyclonal antibodies to other proteins**, it would appear that this region is inherently different from and could not make obvious the claimed peptides with are **immunoreactive with Ro/SSA, not the estrogen receptor.**

Deutscher, et al.

Deutscher, et al., describes the nucleic acid and amino acid sequences of Ro/SSA. There is no disclosure regarding the antigenicity of any portion of the protein, nor does Deutscher,

et al., suggest determining if any one or more particular peptide fragments of the protein are immunoreactive with autoantibody.

Voller, et al.

Voller, et al., describes enzyme-linked immunabsorbent assays using antigen and enzyme labelled antibody. There is no disclosure that one should use octapeptides from a large autoantigen to make a diagnostic assay.

Geyson, et al.

Geyson, et al., discloses a method which was **modified** by appellant to identify the claimed peptides, but which has not otherwise been successfully used by others due to technical difficulties and lack of reproducibility. See, for example, Miller, F.W., K.A. Waite, T. Biswas, P.H. Plotz, "Role of an Autoantigen, Histidyl-tRNA Synthase, in the Induction and Maintenance of Autoimmunity" (1990) Proc. Natl. Acad. Sci. USA 87, 9033-9037. Miller, et al., made hexapeptides of another autoantigen, histidyl tRNA synthase, which is present in approximately 30% of patients with polymyositis. They were unable to obtain any peptides bound by the naturally occurring autoantibodies.

c. The differences between the invention and the cited art.

None of the prior art discloses that autoantigens could have many epitopes, not just one or a few, reactive with autoantibodies.

None of the prior art discloses the claimed peptides; none of the prior art discloses an assay for diagnosing patients with autoantibodies using a peptide based diagnostic assay.

Certainly none of the prior art discloses epitope spreading in patients with autoimmune disease and that peptides of the type defined by appellant might be useful in such as assay.

d. The lack of motivation in the references to combine the art and modify it as appellant has done.

For the claimed peptides and method of use thereof to be obvious, one skilled in the art would have to have been motivated to take the Ro/SSA protein of Deutscher, et al., decide that the protein contains numerous epitopes detectably reactive with autoantibodies in patients reactive with the Ro/SSA protein, exclude all of the peptides that are not reactive as determined empirically by appellant, using a modification of the method of Geyson, et al.

It is unfathomable to the undersigned of any relevance Wotiz has to the claimed subject matter, since none of the peptides are a zinc binding finger and the reference refers to the specificity and lack of cross reactivity of their particular motif.

It is not obvious that one would be able to use the method of Geyson, et al., with any degree of predictability with any large protein, especially a large autoantigen such as Ro/SSA. It may be that tertiary structure is the controlling factor in determining the specificity of the naturally occurring autoantibodies, rather than secondary and tertiary structure.

The bottom line is that the only way to determine that one could isolate and identify short, specific epitopes derived from natural autoantigens which were reactive with autoantibodies was by doing what appellant did, empirically and with absolute no predictability prior to actually doing the work. Even if it was arguably obvious to try (which appellant firmly believes it was not), there was simply no predictability of success.

e. *The difference between the combination of the prior art and appellant's claimed peptides and methods of use thereof.*

Appellant did determine that certain peptides derived from Ro/SSA are reactive with naturally occurring autoantibodies and are therefore useful in diagnosis of patients. This could

not have been obvious to one of ordinary skill in the art, from the cited publications, as of the time this application was filed since it was only by actually synthesizing and testing each peptide can one determine which, if any, peptides derived from the full length protein, will be reactive.

However, assuming one can create the motivation to combine where there is none, had one applied the method of Geyson to the protein of Deutscher, et al., one still would not have had the claimed peptides. One might or might not have obtained some or any of the peptides. One would still have had to select the correct reaction conditions, the selection conditions and patient sera for what constitutes binding (i.e., greater than two standard deviations above normal). One could have been misled by the abundance of literature which said there should only be a few epitopes. One might have selected hexapeptides or decapeptides and ended up with other epitopes than those claimed.

It is well established that for the claimed reagents and methods of use to be obvious from the prior art, there must be a disclose of the elements, motivation to combine, and some predictability of success. See, for example, ACS Hospital Systems, Inc. v. Montefiore Hospital et al. 221 U.S.P.Q. 929 (Fed. Cir. 1984). The test for obviousness requires that one compare the claimed "subject matter as a whole" with the prior art "to which said subject matter pertains" 35 U.S.C. §103.

'The inquiry is thus highly fact-specific by design." In re Ochiai 37 U.S.P.Q.2d 1127, 1131 (Fed. Cir. 1995). In this case, the claimed peptides are highly analogous to the claimed nucleotide molecules in In re Deuel, 34 U.S.P.Q. 1210 (Fed. Cir. 1995), where the Court found that the existence of a general method of isolating cDNA or DNA molecules is irrelevant to whether the specific molecules themselves would have been obvious.

f. Summary.

In summary, the prior art fails to provide the starting materials and process which would predictably lead to the claimed peptides and methods, the motivation to modify and combine the art in the way appellant has done, and the peptides as claimed. None of the art suggests that the large autoantigen, Ro/SSA, could be partitioned into overlapping octapeptides that would be reactive with naturally occurring autoantibodies, nor that the binding would be sufficiently strong and specific to be useful in a diagnostic assay. It is not enough under §103 to use hindsight after applicant has disclosed his invention to piecemeal together the prior art to yield the claimed invention: it must be obvious from the combination of the prior art, as a whole, that one of ordinary skill in the art **should** combine the cited art and would have a **reasonable expectation of success in obtaining the claimed**

very specific peptides and methods of use thereof. The art does not do this.

9. Relief Requested.

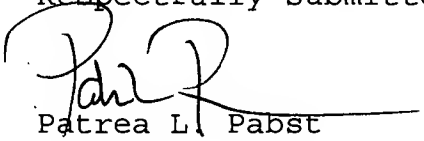
Appellant earnestly solicits the Board to hold that

(a) The claims are definite under 35 U.S.C. §112.

(b) The claims are enabled by the specification under 35 U.S.C. §112, first paragraph; and

(c) The claims are not obvious under 35 U.S.C. §103 over Deutscher, et al., Proc. Natl. Acad. Sci. USA 85, 9479-9483 (1988) in view of U.S. Patent No. 5,312,752 to Wotiz, et al., Voller, et al., Manual of Clin. Lab. Immunol. Chap. 17 (1986) and Geysen, et al. J. Immunol. Methods. 102, 259-271 (1987).

Respectfully submitted,



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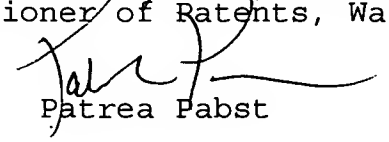

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